



van Vugt, V. A., Bas, G., van der Wouden, J. C., Dros, J., van Weert, H. C. P. M., Yardley, L., Twisk, J. W. R., van der Horst, H. E., & Maarsingh, O. R. (2020). Prognosis and Survival of Older Patients With Dizziness in Primary Care: a 10-year prospective cohort study. *Annals of Family Medicine*, 18(2), 100-109.
<https://doi.org/10.1370/afm.2478>

Peer reviewed version

Link to published version (if available):
[10.1370/afm.2478](https://doi.org/10.1370/afm.2478)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via *Annals of Family Medicine* at <http://www.annfammed.org/content/18/2/100> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

**Prognosis and survival of older dizzy patients in primary care: a 10-year
prospective cohort study**

Vincent A. van Vugt¹, Gülsün Bas¹, Johannes C. van der Wouden¹, Jacqueliën Dros²,
Henk C. P. M. van Weert², Lucy Yardley³, Jos W. R. Twisk⁴, Henriëtte E. van der Horst¹,
Otto R. Maarsingh¹

¹ Amsterdam UMC, Vrije Universiteit Amsterdam, Department of general practice and elderly care medicine, Amsterdam Public Health, de Boelelaan 1117, Amsterdam, Netherlands

² Amsterdam UMC, location AMC, Department of general practice, Amsterdam Public Health, Meibergdreef 9, Amsterdam, Netherlands

³ University of Southampton, Department of Psychology, Southampton, UK.

⁴ Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Epidemiology and Biostatistics, Amsterdam Public Health, de Boelelaan 1117, Amsterdam, Netherlands

Corresponding author:

Vincent A. van Vugt, MD
Amsterdam UMC - Location VUMC
Department of general practice and elderly care medicine
Van der Boechorststraat 7, room C-378. 1081 BT Amsterdam, The Netherlands
Phone: +31613275226
Email: v.vanvugt@vumc.nl

Number of Tables: 10

Number of Figures: 3

Keywords: general practice, primary care, dizziness, vertigo, mortality, prognosis

Pages: 21

Word count: 3005

Disclosures: none

Abstract

Purpose The prognosis of dizzy older patients in primary care is unknown. Our objective was to determine the prognosis and survival of patients with different subtypes and causes of dizziness.

Methods In a primary care prospective cohort study, 417 older adults with dizziness (mean age 75.5 years) received a full diagnostic workup in 2006-2008. A panel of physicians classified their dizziness subtype and primary cause of dizziness. Presyncope was the most common dizziness subtype (69.1%), followed by vertigo (41.0%), disequilibrium (39.8%), and other dizziness (1.7%). The most common primary causes of dizziness were cardiovascular disease (56.8%) and peripheral vestibular disease (14.4%). Main outcome measures were mortality and dizziness-related impairment assessed at 10-year follow-up.

Results At 10-year follow-up 169 patients (40.5%) had died. Multivariable adjusted Cox models showed a lower mortality rate for patients with the subtype vertigo compared to other subtypes (HR 0.62 (95% CI 0.40 to 0.96)), and for peripheral vestibular disease versus cardiovascular disease as primary cause of dizziness (HR 0.46 (95% CI 0.25 to 0.84)). After 10 years, 47.7% of patients who filled out the follow-up measurement experienced substantial dizziness-related impairment. No significant difference in substantial impairment was seen between different subtypes and primary causes of dizziness.

Conclusions The 10-year mortality rate was lower for the dizziness subtype vertigo compared to other subtypes. Patients with dizziness primarily caused by peripheral vestibular disease had a lower mortality rate than patients with cardiovascular disease.

Substantial dizziness-related impairment in older dizzy patients 10 years later is high, and indicates that current treatment strategies by FPs may be suboptimal.

Introduction

Dizziness is a common problem among older patients in primary care (1). The annual prevalence of dizziness in adults ranges between 20-30% in population-based questionnaire studies (2). The frequency and severity of dizziness symptoms generally increase with age (3). Diagnosing dizziness and estimating its prognosis is a complex problem for clinicians (4). Dizziness is a subjective sensation, only measurable by self-report, that can be caused by a broad array of benign but also by serious medical conditions. The diagnostic process is particularly challenging in dizzy older patients, because the cause of their dizziness is mostly multifactorial (5, 6). Dizziness is often divided in four major subtypes: vertigo, presyncope (also known as light-headedness), disequilibrium (also known as unsteadiness) and other dizziness (7-9). Different subtypes are generally associated with different organ systems such as peripheral vestibular disease or cardiovascular disease (4, 5). Determining the cause of dizziness might help in choosing an appropriate treatment.

Over 80% of patients experiencing dizziness in The Netherlands, UK and USA are primarily treated by their primary care physician and are never referred to a specialist (10-12). Nevertheless, most diagnostic and prognostic studies investigated patients in secondary and tertiary care settings (13-15). We started a prospective cohort study in 2006 to gain more insight in the diagnosis and prognosis of older dizzy patients in primary care (5). This study already yielded new insights into diagnosing dizziness in primary care that have been reported in previous publications (5, 16, 17). By following these patients over a 10-year period we are now also able to investigate the long-term

prognosis of older dizzy patients in primary care. Dizziness has been associated with increased premature mortality (18) and substantial functional impairment (16, 19), but it is unclear if these risks are equal for all subtypes and causes of dizziness. More specific prognostic information may help family physicians to timely identify and treat high-risk patients. The objective of this study is to investigate if and how the dizziness subtypes and primary causes of dizziness are associated with mortality and dizziness-related impairment 10 years later.

Methods

Participants and baseline assessments

The details of the inclusion and baseline data collection of the Dizziness In Elderly Patients (DIEP) cohort were reported previously (5, 20). In summary, we prospectively identified 417 older primary care patients (aged ≥ 65 years) with dizziness that had been present for at least two weeks from June 2006 to January 2008. An international Delphi procedure was used to determine a comprehensive list of useful diagnostic dizziness tests. At inclusion all patients received this full diagnostic workup. We recorded sociodemographic characteristics, smoking habits, alcohol intake, current use of medication, medical history, characteristics of dizziness, and the use of a hearing, seeing, or walking aid. All patients had to complete the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (PHQ), a self-administered instrument to assess psychiatric disorders (21, 22). During the physical examination we assessed the following organ systems: cardiovascular (pulse, blood pressure, orthostatic hypotension measurement), locomotor (orthopaedic screening of lower limbs, tandem

gait, timed up-and-go test), neurological (tendon reflexes, Semmes-Weinstein monofilament test), vestibular (otoscopy, Dix-Hallpike manoeuvre, audiometry) and visual (Landolt rings eye chart). We also tested haemoglobin and non-fasting blood glucose levels in the laboratory and performed an electrocardiogram and continuous event recording on indication. Next, a panel consisting of a family physician, a geriatrician and a nursing home physician independently reviewed the data for each patient to ascertain dizziness subtype and (major and minor contributory) causes of dizziness. Every participant was definitively categorized into one or more of the four dizziness subtypes by means of a majority decision (at least two of three panel members had to agree). In addition, the panel classified the relative contribution (from 0% to 100%) of causes of dizziness for each patient from a list of nine possible groups of medical conditions: cardiovascular disease (including cerebrovascular disease), peripheral vestibular disease, psychiatric disease, locomotor disease, neurological disease (excluding cerebrovascular disease), adverse drug effect, metabolic or endocrine conditions, impaired vision and other cause. All causes that were scored higher than 0% by at least two out of three panel members were considered as a contributory cause. The medical condition with the highest mean contributing percentage across all three reviewers was identified as the primary cause of dizziness (5).

Follow-up

Our primary outcomes are mortality and significant impairment due to dizziness. The follow-up measurements took place between October 2016 and January 2018, approximately 10 years after the start of the study. Deaths were identified through FP

records and reports by next of kin. Patients lost to follow-up were censored at the last day confirmed to be alive. When the exact day of death was unclear, we entered the middle of the known month or year as date of death. We used the Dizziness Handicap Inventory (DHI) to assess impairment due to dizziness (23). The DHI is the most widely used questionnaire for dizziness and can be used to quantify self-perceived impact of dizziness on daily life (24). It has been shown to have good construct validity, high internal consistency, and satisfactory test-retest reliability (23, 25-27). The questionnaire consists of 25 questions (score range 0-100); higher scores correspond with more handicapping effects due to dizziness. A total DHI-score of 30 or higher is generally believed to indicate substantial dizziness-related impairment (25, 28, 29). Participants were asked to fill out a DHI questionnaire at baseline, and after six months (30) and 10 year follow-up. Participants who were mentally or physically unable to complete a questionnaire were excluded.

Statistical analyses

To analyse the relationship between dizziness and mortality, first we calculated the time to event from the date of enrolment in the DIEP cohort to date of death or the end of follow-up, whichever came first. Second, we generated Kaplan Meier survival curves for the four dizziness subtypes and compared them with log rank tests. Third, we performed Cox proportional hazard models to estimate hazard ratios with 95% confidence intervals for the four different dizziness subtypes and for the nine primary causes. Based on previous studies and feasibility, we pre-specified the following potential confounders: age (18, 31-33), sex (18, 31-33), ethnicity (18, 31), level of education (18, 31), pre-

existent cardiovascular disease (18, 32), pre-existent stroke (18, 32), pre-existent diabetes (18, 30), polypharmacy (defined as >5 types of daily medication) (30, 32, 34), a comorbid anxiety or depressive disorder at baseline according to the PRIME-MD PHQ (30-32, 35) and the number of assigned dizziness subtypes. The ten potential confounders are described in more detail in Supplementary Appendix 1. We adjusted for these pre-specified potential confounders by adding them as covariates to the models. To analyse the relationship with dizziness-related impairment, we used total DHI-scores at baseline, six-month follow-up and 10-year follow-up as outcome. These scores were analysed both as a continuous variable and a dichotomous variable (i.e. no substantial impairment [DHI scores between 0 and 29] and substantial impairment [DHI scores between 30 and 100]). For the continuous outcome we used linear mixed model analysis, and for dichotomous outcome we used logistic generalized estimating equations (GEE analysis) (36). Both methods take into account the dependency of the observations within the patient. In both analyses, we adjusted for the same pre-specified potential confounders as for the Cox proportional hazard models. We also conducted one exploratory analysis and two post hoc sensitivity analyses to test the robustness of our findings. In the exploratory analysis, we graphically illustrated how participants who filled out the 10-year DHI measurement tracked over all three time points. In the first sensitivity analysis, the dizziness subtype in patients had to be agreed upon by all three panel physicians (unanimous decision) instead of at least two out of three panel physicians (majority decision). In the second sensitivity analysis, only participants who were assigned to one subtype were included in the analyses. SPSS 22.0 and Stata 14.1 were used for statistical analyses.

Results

Study participants

The DIEP cohort consists of 417 participants. At baseline, the mean age of participants was 78.5 years (range 65-95); 74% were female and 69% had experienced dizziness for more than six months. Presyncope was the most common dizziness subtype (69.1%), followed by vertigo (41.1%), disequilibrium (39.8%), and other dizziness (1.7%). Patients were assigned by the panel to one subtype (52.0%), two subtypes (32.9%), three subtypes (11.3%) or no subtype at all (3.8%). According to the panel, the most common primary causes of dizziness were cardiovascular disease (56.8%), and peripheral vestibular disease (14.4%). The baseline characteristics are presented in Table 1. After 10 years, 103 participants (24.7%) filled out a DHI and could be analysed for dizziness-related impairment. Of the other participants 169 (40.5%) had died, 86 (20.6%) had no known address or did not respond to the questionnaire, 30 (7.2%) suffered from serious cognitive disorders, 21 (5.0%) were contacted but refused to participate and 8 (1.9%) had severe somatic disorders, such as a terminal illness, that prevented them from filling out a questionnaire.

Mortality

At 10-year follow-up 169 deaths were recorded (40.5%). The association between mortality and dizziness subtypes is shown in Table 2, before and after adjusting for potential confounders. Participants with the subtype vertigo had a lower 10-year mortality risk (hazard ratio 0.62, 95% confidence interval 0.40 to 0.96) than participants with other dizziness subtypes. The Kaplan-Meier survival curve in Figure 1 further illustrates this

association. Table 3 and Figure 2 show the association between mortality and the primary cause of dizziness, again before and after adjusting for potential confounders. Dizziness due to peripheral vestibular disease was associated with a lower hazard of death (hazard ratio 0.46, 95% confidence interval 0.25 to 0.84) than dizziness due to cardiovascular disease.

Dizziness-related impairment

An overview of DHI-scores for each measurement moment is presented in Table 4. At baseline, the mean DHI-score was 36.3 and 60.7% of participants had a DHI-score ≥ 30 which constitutes substantial impairment due to dizziness. After 10 years, the average DHI-score was 31.1 and 47.4% of the 103 participants still experienced substantial dizziness-related impairment. Approximately one third (34%) of these participants never reported substantial dizziness-related impairment, while one fourth (26%) experienced this at every measurement.

Table 5 shows the association between dizziness subtypes and dizziness-related impairment 10 years later. The dizziness subtype presyncope was associated with a lower mean DHI-score than in participants without this subtype, but not with a significant lower odds at substantial dizziness-related impairment. Other subtypes were not significantly associated with DHI-scores, nor were the different primary causes of dizziness such as vascular or peripheral vestibular disease. The relationship between these primary causes and impairment is shown in Table 6.

Exploratory and sensitivity analyses

In Supplementary Appendix 2, we listed the baseline characteristics of patients who were still alive and had died during follow-up. Compared to deceased patients, patients who were alive at follow-up were younger, more often female and used more medication. In Supplementary Appendix 3, we listed the baseline characteristics of alive patients at follow-up who filled out the 10-year DHI measurement versus patients who did not. In an exploratory analysis, we used the DHI total score of each of the 103 participants at the baseline, six month and 10-year measurement to analyse how scores tracked over time. As graphically shown in Supplementary Figure 1, no clear pattern can be identified in these scores.

In the first sensitivity analysis, the dizziness subtype in patients had to be agreed upon by all three panel physicians (unanimous decision) instead of at least two out of three panel physicians (majority decision). Supplementary Tables 1 and 2 show the association of unanimous dizziness subtypes with mortality and dizziness-related impairment 10 years later. The associations of unanimous subtypes with mortality were comparable to the main analysis, but failed to reach statistical significance due to larger confidence intervals. Unlike the majority decision subtype presyncope, the unanimous subtype presyncope was not associated with DHI-score. In the second sensitivity analysis, only participants who were assigned to one subtype (N=217) were included in the analyses. Supplementary Tables 3 and 4 show the associations between dizziness subtypes with mortality and dizziness-related impairment 10 years later in this group of patients. The

associations are similar to the main analysis, but due to the small number of patients in this analysis no significant associations were seen.

Discussion

Summary

In a prospective 10-year cohort study in primary care with older patients with panel-diagnosed dizziness, we analysed the association of different subtypes and primary causes of dizziness with mortality and dizziness-related impairment. The dizziness subtype vertigo was associated with a lower mortality rate in the 10-year period than the subtypes presyncope, disequilibrium and other dizziness. Dizziness due to peripheral vestibular disease was associated with a lower risk of mortality in 10 years than dizziness due to cardiovascular disease. Although subtypes and primary causes of dizziness were not significantly associated with the development of substantial impairment due to dizziness, participants with the presyncope subtype did have relatively less dizziness symptoms 10 years later. A final notable finding was that even though dizziness is often seen as a self-limiting affliction, almost half of all participants who filled out the 10-year measurement felt substantially impaired due to dizziness.

Comparison with existing literature

In a large American population-based cohort study the presence of dizziness in the last 12 months was an independent risk factor for mortality (18). After adjusting for relevant covariates including age, ethnicity, race, gender, diabetes, cardiovascular, cerebrovascular disease and cancer, being dizzy was a risk factor for early mortality comparable to leading causes of death such as cardiovascular disease and cancer (18). This is the first study that examines differences in mortality for subtypes and causes of dizziness. We found that the vertigo subtype and dizziness primarily due to peripheral

vestibular disease were associated with a lower mortality rate in a 10-year period. Intuitively, this might not be surprising because vertigo patients and patients with peripheral vestibular disease are younger on average and more often female than presyncope patients and patients with cardiovascular disease (5). Nevertheless, these associations remained significant after adjusting for age, gender and other confounders. Research on the prognosis of dizziness in primary care is scarce (37). Most epidemiological studies in community-dwelling older adults have been cross-sectional (2). Only three long-term prospective cohort studies (>1 year) were identified and none of these studies measured dizziness-related impairment longitudinally (31-33). Our study found less dizziness-related impairment in presyncope patients, but not less substantial dizziness-related impairment ($DHI \geq 30$). This is the first prognostic longitudinal study that identifies a difference in dizziness-related impairment between subtypes. These results should be interpreted with caution though, because they might be explained by the higher mortality rate in the presyncope group (survivor bias (38)). No other associations between dizziness-related impairment and subtypes or primary causes of dizziness were identified. Overall, 47.7% of patients who filled out the 10-year measurement experienced substantial dizziness-related impairment. This suggests that current treatment strategies in primary care may be suboptimal.

Strengths and limitations

Our study has several strengths. An extensive diagnostic set of tests for dizziness was developed based on a systematic review and a Delphi procedure with experts in the field (20). All participants completed this workup and were then diagnosed by a panel of three

physicians, which is the preferred diagnostic method when a gold standard is not available (39). Considering this time-intensive inclusion process, we managed to include a sizeable cohort of 417 participants.

There are also some limitations. First, Drachman's categorization in four subtypes is still widely used, but not undisputed. There is a risk of misdiagnosis when we only focus on the way patients describe their dizziness, e.g. a "spinning sensation" or "light-headedness". At the moment, a paradigm shift in diagnosing dizziness is taking place which focuses less on the patients' description of their dizziness sensation and more on timing and triggers (40, 41). New terminology has been proposed, but in most guidelines dizzy patients are still categorized according to the classical four subtypes (8, 9). Our panel did not base their diagnosis on the patients' description of dizziness but on a comprehensive set of diagnostic tests and an extensive medical history including timing and triggers. Therefore, future changes in nomenclature and diagnostic procedures will not directly invalidate the results of our study. General practitioners will continue to have to assess the primary cause of dizziness and identify patients at risk for persistent impairment due to dizziness (28). Second, we adjusted in our analyses for ten potential confounders. To limit the risk of bias, covariates were defined before we conducted our analyses. We chose these confounders based on feasibility and a literature review of previous studies (18, 30-35). Although we have attempted to adjust for the most relevant confounders, we cannot exclude the possibility that unidentified factors influenced our primary outcomes. Third, due to the advanced age of our participants at inclusion, only a limited subset was available for analysis of dizziness-related impairment 10 years later. This small sample size might be why we found no significant differences between

different primary causes of dizziness. In the main analysis, the dizziness subtype presyncope, as determined by a majority decision of the panel, was associated with a lower mean DHI-score 10 years later. However, in a sensitivity analysis that only assigned patients to a subtype if all three panel members agreed, the subtype presyncope was not associated with the DHI-score. This indicates that the results we found on the association between different dizziness subtypes and long-term dizziness-related impairment should be interpreted with care.

Conclusions and implications for research and/or practice

These results provide new insights in the prognosis of older dizzy patients in primary care. The 10-year survival was higher for patients with the subtype vertigo compared to other subtypes. Patients with dizziness primarily caused by peripheral vestibular disease also lived longer than patients with dizziness caused by vascular disease. Differences in subtype and primary cause of dizziness were not associated with substantial dizziness-related impairment 10 years later. The large percentage of older dizzy patients that experience substantial dizziness-related impairment 10 years later indicates that current treatment strategies in primary care may be suboptimal.

Additional information

1. Acknowledgements

We would like to thank Welmoed Krib for her help in collecting the 10-year follow-up data.

2. Competing interests

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

3. Funding

This study was funded by a Amsterdam Public Health Aging And Later Life innovation grant and by the Netherlands Organisation for Health Research and Development (ZonMW, No. 4200.0018), The Hague. The sponsors did not participate in the study design, data collection, analysis, interpretation, or the preparation or submission of this report.

4. Ethical approval

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center. All patients included in the study provided written informed consent.

5. Contributors

Contributors: VAvV and ORM developed the concept of the article. ORM, JD, GB and VAvV collected the data. VAvV and JWRT analyzed the data. VAvV wrote the first substantial draft of the article and is the guarantor. JCvdW, HEvdH, HCPMvW and LY critically revised the manuscript. All authors read and approved the final manuscript.

References

1. Bailey KE, Sloane PD, Mitchell M, Preisser J. Which primary care patients with dizziness will develop persistent impairment? *Arch Fam Med*. 1993;2(8):847-52.
2. Neuhauser HK. The epidemiology of dizziness and vertigo. *Handb Clin Neurol*. 2016;137:67-82.
3. Jonsson R, Sixt E, Landahl S, Rosenhall U. Prevalence of dizziness and vertigo in an urban elderly population. *J Vestib Res*. 2004;14(1):47-52.
4. Sloane PD, Coeytaux RR, Beck RS, Dallara J. Dizziness: state of the science. *Ann Intern Med*. 2001;134(9 Pt 2):823-32.
5. Maarsingh OR, Dros J, Schellevis FG, van Weert HC, van der Windt DA, ter Riet G, et al. Causes of persistent dizziness in elderly patients in primary care. *Ann Fam Med*. 2010;8(3):196-205.
6. Tinetti ME, Williams CS, Gill TM. Dizziness among older adults: a possible geriatric syndrome. *Ann Intern Med*. 2000;132(5):337-44.
7. Drachman DA, Hart CW. An approach to the dizzy patient. *Neurology*. 1972;22(4):323-34.
8. Branch W. Approach to the patient with dizziness [updated November 2014]. Available from: www.uptodate.com.
9. [Summary of the Dutch College of General Practitioners' practice guideline 'Dizziness']
https://www.nhg.org/system/files/content/nhg_org/uploads/standaard/pdf/m75_2.pdf
2017
10. Sloane PD, Dallara J, Roach C, Bailey KE, Mitchell M, McNutt R. Management of dizziness in primary care. *J Am Board Fam Pract*. 1994;7(1):1-8.
11. Hanley K, T OD. Symptoms of vertigo in general practice: a prospective study of diagnosis. *Br J Gen Pract*. 2002;52(483):809-12.
12. Stam H, Harting T, Sluijs M, Marum R, Horst H, Wouden JC, et al. Usual care and management of fall risk increasing drugs in older dizzy patients in Dutch general practice. *Scand J Prim Health Care*. 2016;34(2):165-71.
13. Brandt T, Huppert T, Hufner K, Zingler VC, Dieterich M, Strupp M. Long-term course and relapses of vestibular and balance disorders. *Restor Neurol Neurosci*. 2010;28(1):69-82.
14. Strupp M, Dieterich M, Brandt T. The treatment and natural course of peripheral and central vertigo. *Dtsch Arztebl Int*. 2013;110(29-30):505-15; quiz 15-6.
15. Obermann M, Bock E, Sabev N, Lehmann N, Weber R, Gerwig M, et al. Long-term outcome of vertigo and dizziness associated disorders following treatment in specialized tertiary care: the Dizziness and Vertigo Registry (DiVeR) Study. *J Neurol*. 2015;262(9):2083-91.
16. Dros J, Maarsingh OR, Beem L, van der Horst HE, ter Riet G, Schellevis FG, et al. Impact of dizziness on everyday life in older primary care patients: a cross-sectional study. *Health Qual Life Outcomes*. 2011;9:44.

17. Dros J, Maarsingh OR, van der Windt DA, Oort FJ, ter Riet G, de Rooij SE, et al. Profiling dizziness in older primary care patients: an empirical study. *PLoS One*. 2011;6(1):e16481.
18. Corrales CE, Bhattacharyya N. Dizziness and death: An imbalance in mortality. *Laryngoscope*. 2016;126(9):2134-6.
19. Mueller M, Strobl R, Jahn K, Linkohr B, Peters A, Grill E. Burden of disability attributable to vertigo and dizziness in the aged: results from the KORA-Age study. *Eur J Public Health*. 2014;24(5):802-7.
20. Maarsingh OR, Dros J, van Weert HC, Schellevis FG, Bindels PJ, van der Horst HE. Development of a diagnostic protocol for dizziness in elderly patients in general practice: a Delphi procedure. *BMC Fam Pract*. 2009;10:12.
21. Spitzer RL, Kroenke K, Linzer M, Hahn SR, Williams JB, deGruy FV, 3rd, et al. Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 Study. *JAMA*. 1995;274(19):1511-7.
22. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282(18):1737-44.
23. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg*. 1990;116(4):424-7.
24. Mutlu B, Serbetcioglu B. Discussion of the dizziness handicap inventory. *J Vestib Res*. 2013;23(6):271-7.
25. Tamber AL, Wilhelmsen KT, Strand LI. Measurement properties of the Dizziness Handicap Inventory by cross-sectional and longitudinal designs. *Health Qual Life Outcomes*. 2009;7:101.
26. Vereeck L, Truijen S, Wuyts F, Van de Heyning PH. Test-retest reliability of the Dutch version of the Dizziness Handicap Inventory. *B-ENT*. 2006;2(2):75-80.
27. Vereeck L, Truijen S, Wuyts FL, Van De Heyning PH. Internal consistency and factor analysis of the Dutch version of the Dizziness Handicap Inventory. *Acta Otolaryngol*. 2007;127(8):788-95.
28. Stam H, Maarsingh OR, Heymans MW, van Weert H, van der Wouden JC, van der Horst HE. Predicting an Unfavorable Course of Dizziness in Older Patients. *Ann Fam Med*. 2018;16(5):428-35.
29. Whitney SL, Wrisley DM, Brown KE, Furman JM. Is perception of handicap related to functional performance in persons with vestibular dysfunction? *Otol Neurotol*. 2004;25(2):139-43.
30. Dros J, Maarsingh OR, Beem L, van der Horst HE, ter Riet G, Schellevis FG, et al. Functional prognosis of dizziness in older adults in primary care: a prospective cohort study. *J Am Geriatr Soc*. 2012;60(12):2263-9.
31. Maarsingh OR, Stam H, van de Ven PM, van Schoor NM, Ridd MJ, van der Wouden JC. Predictors of dizziness in older persons: a 10-year prospective cohort study in the community. *BMC Geriatr*. 2014;14:133.
32. Gassmann KG, Rupprecht R, Group IZGS. Dizziness in an older community dwelling population: a multifactorial syndrome. *J Nutr Health Aging*. 2009;13(3):278-82.
33. Olsson Moller U, Midlov P, Kristensson J, Ekdahl C, Berglund J, Jakobsson U. Prevalence and predictors of falls and dizziness in people younger and older than 80 years of age--a longitudinal cohort study. *Arch Gerontol Geriatr*. 2013;56(1):160-8.

34. Leelakanok N, Holcombe AL, Lund BC, Gu X, Schweizer ML. Association between polypharmacy and death: A systematic review and meta-analysis. *J Am Pharm Assoc* (2003). 2017;57(6):729-38 e10.
35. Pratt LA, Druss BG, Manderscheid RW, Walker ER. Excess mortality due to depression and anxiety in the United States: results from a nationally representative survey. *Gen Hosp Psychiatry*. 2016;39:39-45.
36. Twisk JW. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. *Eur J Epidemiol*. 2004;19(8):769-76.
37. Bosner S, Schwarm S, Grevenrath P, Schmidt L, Horner K, Beidatsch D, et al. Prevalence, aetiologies and prognosis of the symptom dizziness in primary care - a systematic review. *BMC Fam Pract*. 2018;19(1):33.
38. Austin PC, Mamdani MM, van Walraven C, Tu JV. Quantifying the impact of survivor treatment bias in observational studies. *J Eval Clin Pract*. 2006;12(6):601-12.
39. Rutjes AW, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. *Health Technol Assess*. 2007;11(50):iii, ix-51.
40. Edlow JA, Gurley KL, Newman-Toker DE. A New Diagnostic Approach to the Adult Patient with Acute Dizziness. *J Emerg Med*. 2018;54(4):469-83.
41. Newman-Toker DE, Edlow JA. TiTrATE: A Novel, Evidence-Based Approach to Diagnosing Acute Dizziness and Vertigo. *Neurol Clin*. 2015;33(3):577-99, viii.